

Alpha subunits

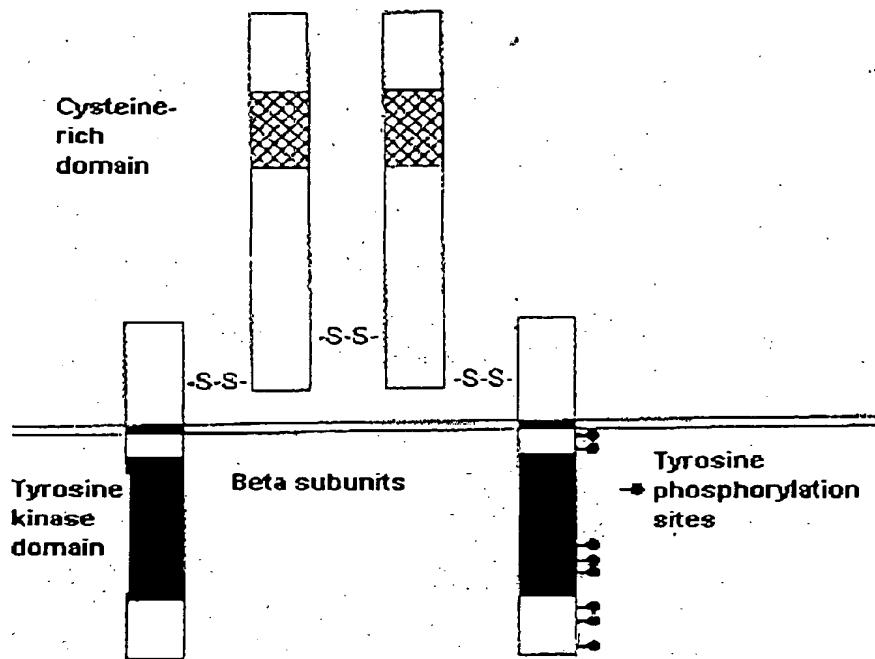


FIGURE 1

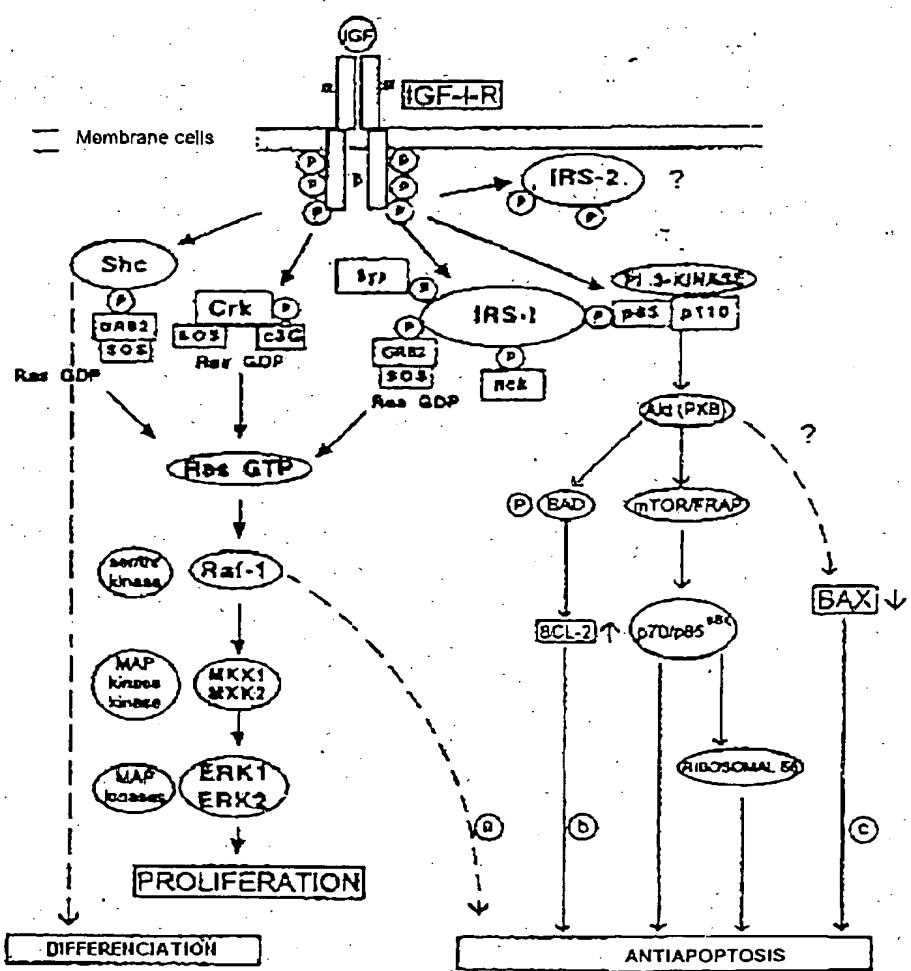


FIGURE 2

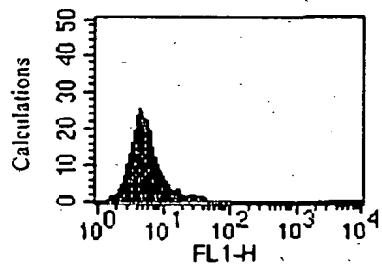


FIGURE 3A

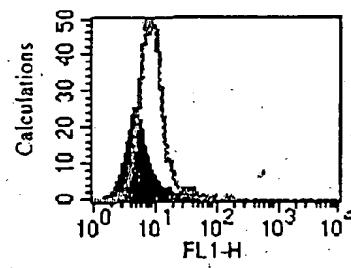


FIGURE 3B

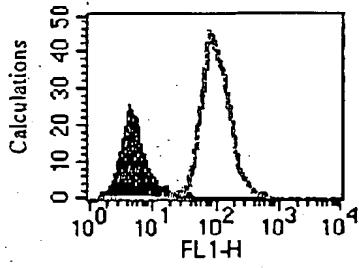
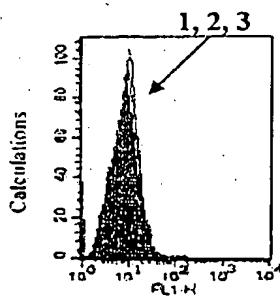
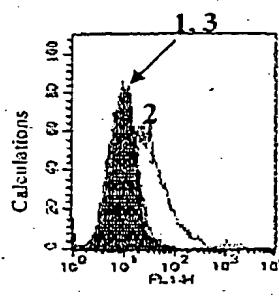


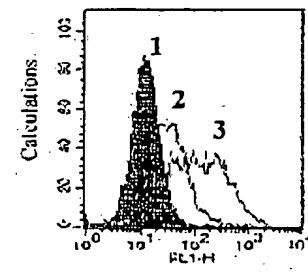
FIGURE 3C



Nontransfected cells



IGF-IR+ cells



IR+ cells

FIGURE 4A

FIGURE 4B

FIGURE 4C

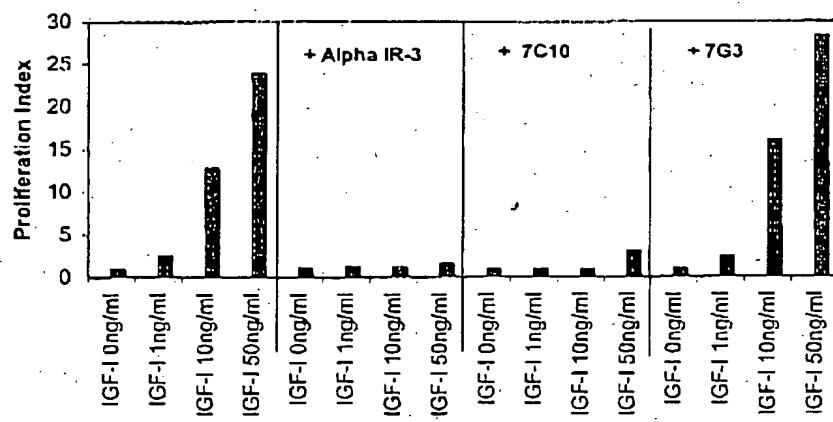


FIGURE 5

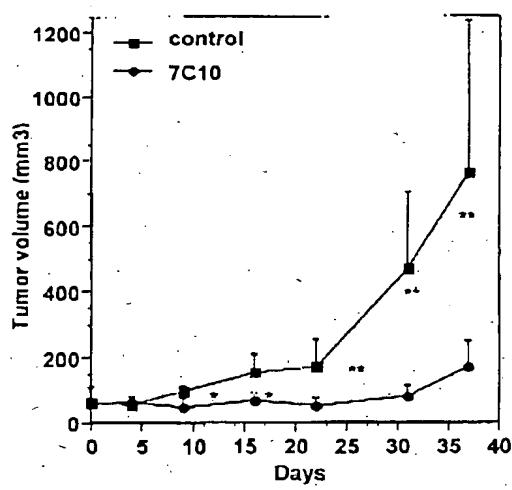


FIGURE 6A

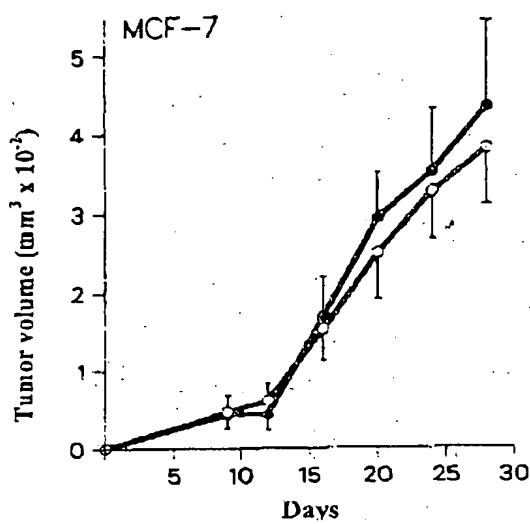


FIGURE 6B

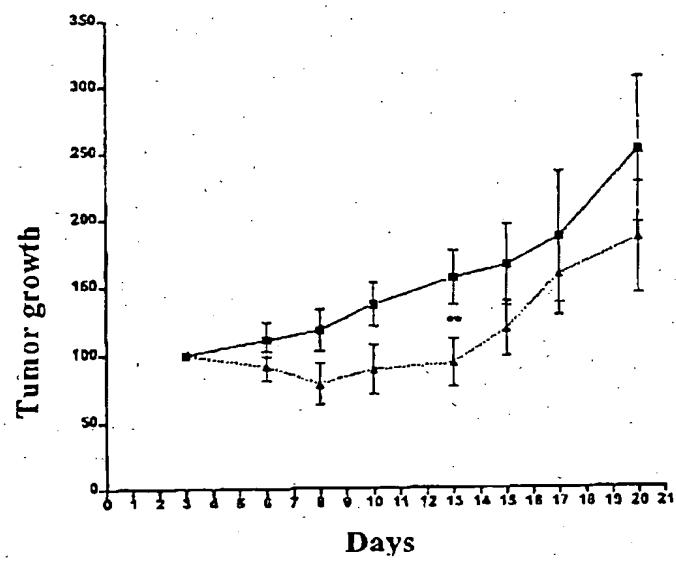


FIGURE 6C

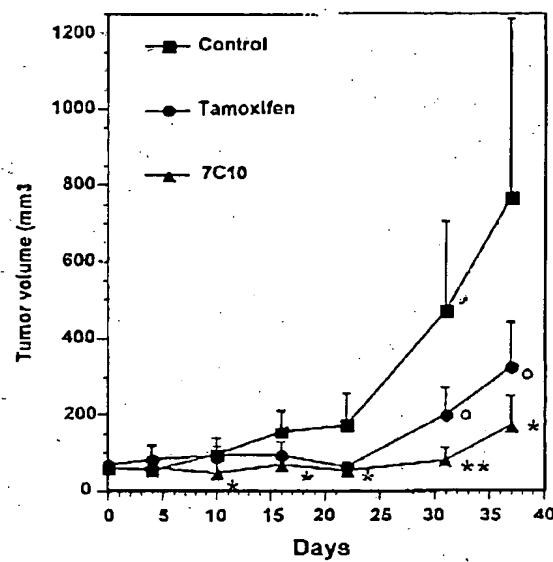


FIGURE 7

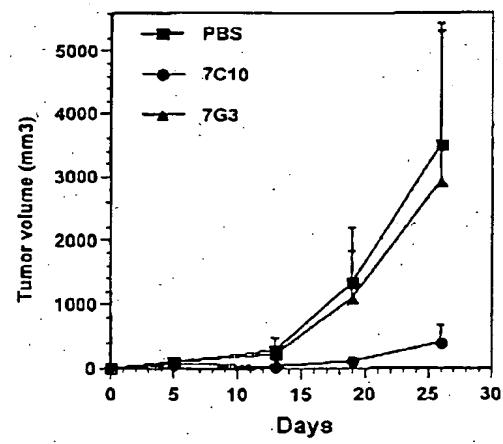


FIGURE 8A

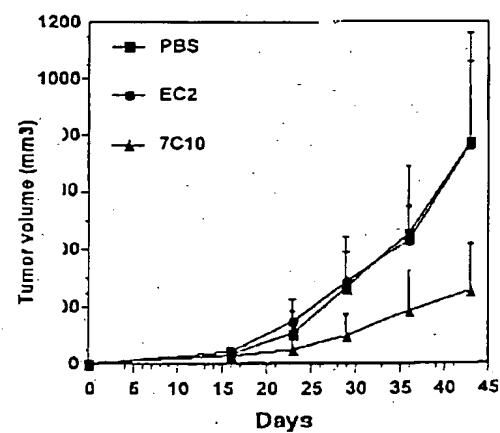


FIGURE 8B

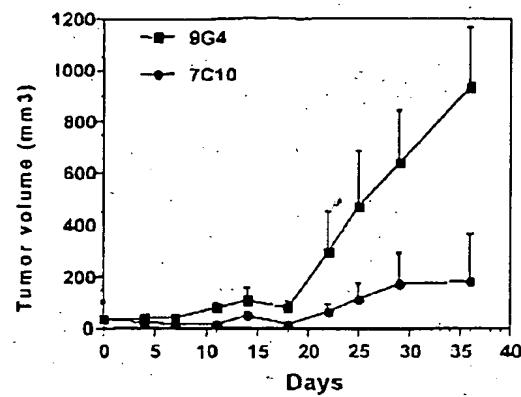


FIGURE 8C

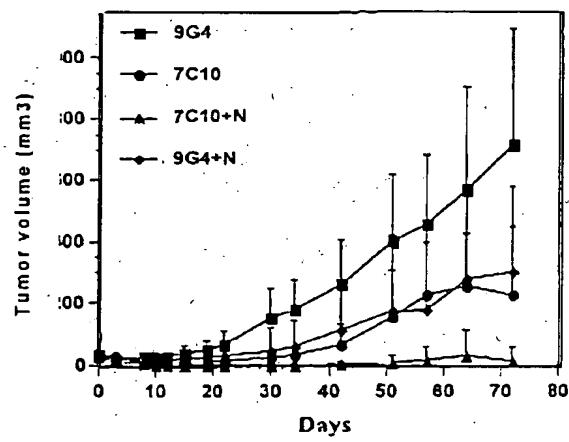


FIGURE 9

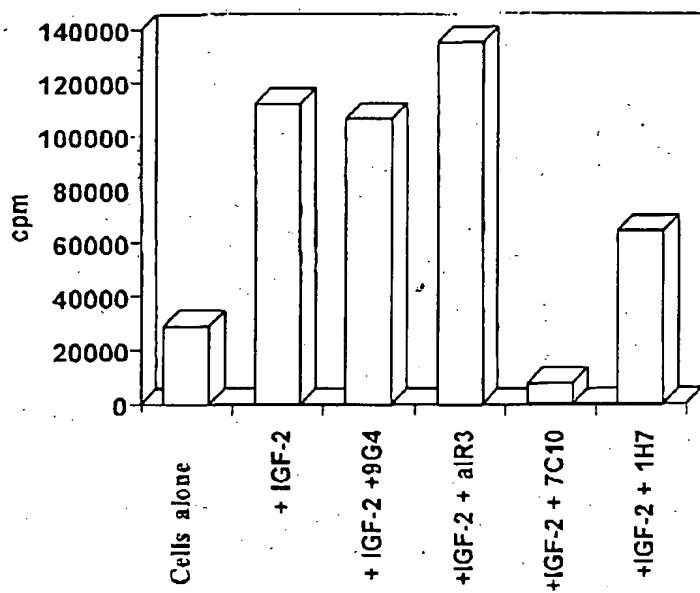


FIGURE 10

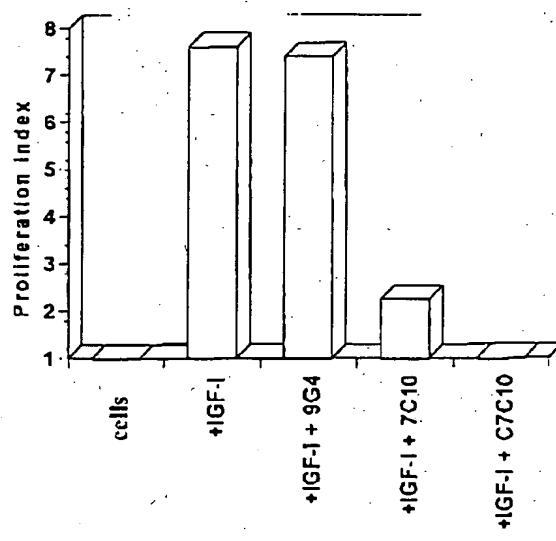


FIGURE 11

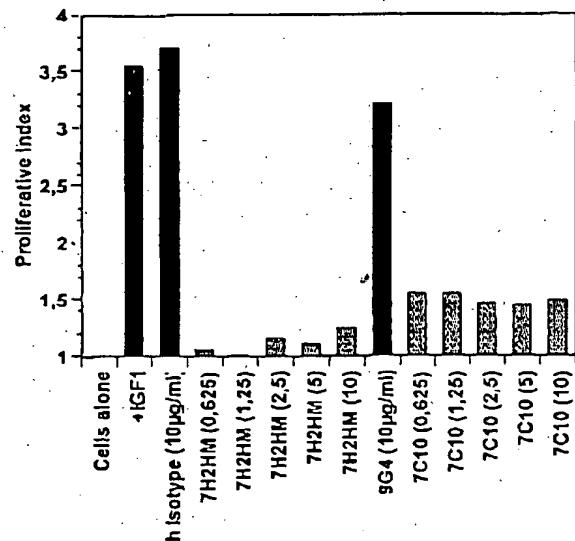


FIGURE 12

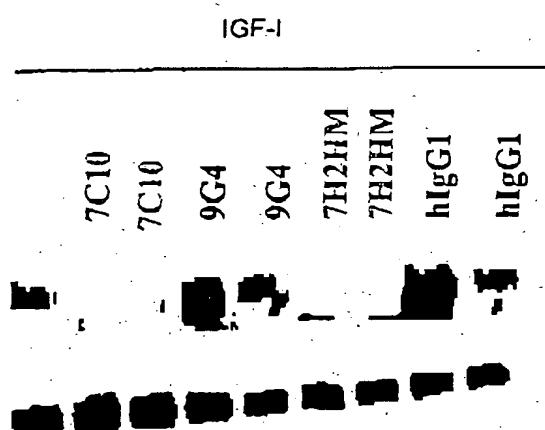


FIGURE 13

ATGAAGTTGCCTGTTACCCCTGTTGGTGTGATGTTCTGGATTCCTGCTTCGAGAAGTGAT
 1 +-----+-----+-----+-----+-----+-----+-----+ 60
 TACTTCAACGGACAATCCGACAACCACCACTACAGACCTAAGGACGAAGTCTCACTA
 ATGAAGTTGCCTGTTAGGCTGTTGGTGTGCT
 oligo MKV-1 L M F W I P A S R S D -
 3' end leader peptide
 GTTTGATGACCCAAATTCCACTCTCCCTGCCTGTCAGTCTGGAGATCAAGCCTCCATC
 61 +-----+-----+-----+-----+-----+-----+-----+ 120
 CAAAACACTGGGTTAAGGTGAGAGGGACGGACAGTCAGAACCTCTAGTCGGAGGTAG
 V L M T Q I P I S L P V S L G D O A S T -
 TCTTCAGATCTAGTCAGAGCATGATGACATAGTAATGAAACACCTATTACATGGTAC
 121 +-----+-----+-----+-----+-----+-----+-----+ 180
 AGAACGTCTAGATCACTCTCGTAACATGTATCATTACCTTGTGGATAATGTTACCATG
 S C R S S O S I V H S N G N T Y L Q W Y -
 CDR 1
 CTCCAGAAACCCAGGTCACTCTCCAAACCTCTGATCTACAAAGTTCCAACCGACTTAT
 181 +-----+-----+-----+-----+-----+-----+-----+ 240
 GACGTCTTGGTCCAGTCAGAGGTTTCGAGGACTACATCTTCAGGGTTGGCTGAAATA
 L Q K P G Q S P K L L I Y K V S N R L Y -
 CDR 2
 GGGGTCCCAGACAGGTTCACTGGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGC
 241 +-----+-----+-----+-----+-----+-----+-----+ 300
 CCCCAGGGTCTGTCCAAGTCACCGTCACCTAGTCCCTGTCTAAACTGTGAGTTCTAGTCG
 G V P D R F S G S G S G T D F T L K I S -
 AGCGTGGAGGCTGAGGATCTGGAGTTATTACTGCTTCAGCTCACATGTTCCGTGC
 301 +-----+-----+-----+-----+-----+-----+-----+ 360
 TCGCACCTCCGACTCCTAGACCCCTCAAATAATGACGAAGTCCAAGTGTACAAGGCACC
 S V E A E D L G V Y Y C F Q G S H V P W -
 CDR 3
 GG
 ACGTTCGGTGGAGGCACCAAGCTGAAATCAAACGGGCTGATGCTGCACCAACTGTATCC
 361 +-----+-----+-----+-----+-----+-----+-----+ 420
 TGCAAGCCACCTCCGTGGTCGACCTTAGTTGCCCGACTACGACGTGGTTGACATAGG
 T F G G G T K L E I K
 MKC oligo
 TAGAAGGGTGGTAGGTCA
 ATCTTCCCACCATCCAGT
 421 +-----+-----+-----+-----+-----+-----+ 438
 TAGAAGGGTGGTAGGTCA

FIGURE 14

1 ATGATGGTCTTAAGTCTTCTGTACCTCTGACAGCCATTCTGGTATCCTGTCTGATGTA 60
 1 TACTACCACAATTCAAGAACATGGACAACTGTCGGTAAGGACCATAGGACAGACTACAT
 MHV-12 ATGATGGTCTTAAGTCTTCTGTACCT
 MHV-8 ATGAGAGTGCTGATTCTTTGTG
 L L T A I P G I L S D V -
 3' end leader peptide
 CAGCTTCAGGAGTCAGGACCTGGCCTCGTGAAACCTTCTCAGTCTGTCTCACCTGC 120
 61 GTCGAAGTCCTCAGTCTGGACCGGAGCACTTGGAAAGAGTCAGAGACAGAGAGTGGACG
 Q L Q E S G P G L V K P S O S L S L T C -
 TCTGTCACCCGGCTACTCCATCACCGGTGGTTATTATGAAACTGGATCCGGCAGTTCCA 180
 121 AGACAGTGGCCCATCACCTAGTGGCCACCAATAAACCTTGACCTAGGCCGTCAAAGGT
 S V T G Y S I T G G Y L W N W I R Q F P -
 CDR 1
 CGAAACAAACTGGAGTGCATGGGCTACATAAGCTACGACGGTACCAATAACTACAAACCA 240
 181 CCTTTGTTGACCTCACCTACCCGATGTATTCCATGCTGCCATGGTTATTGATGTTGGT
 G N K L E W M G Y I S Y D G T N N Y K P -
 CDR 2
 TCTCTCAAAGATCGAATCTCCATCACTCGTGACACATCTAAGAACCAAGTTTCTGAAG 300
 241 AGACAGTTCTAGCTTAGAGGTACTGAGCACTGTGTAGATTCTGGTCAAAAGGACTTC
 S L K D R I S I T R D T S K N Q F F L K -
 TTCAATTCTGTGACTAATGAAGACACAGCTACATATTACTGTGCAAGATACTGGTAGGGTC 360
 301 AACTTAAGACACTGATTACTCTGTGTCGATCTATAATGACACGTTCTATCCCATCCUAG
 I N S V T N E D T A T Y Y C A R Y G R V -
 CDR 3
 GGG
 TTCTTTGACTACTGGGCCAAGGCACCACTCTCACAGTCTCCTCAGCCAAACGACACCC 420
 361 AAGAAAATGATGACCCCGGTTCCGTGGTAGAGGTGTCAGAGGAGTCGGTTTGCTGGG
 F F D Y W G Q G T T L T V S S
 oligo MHC-1
 GGTAGACAGATAGGTGAC
 CCATCTGTCTATCCACTG
 421 GGTAGACACATAGGTGAC 438

FIGURE 15

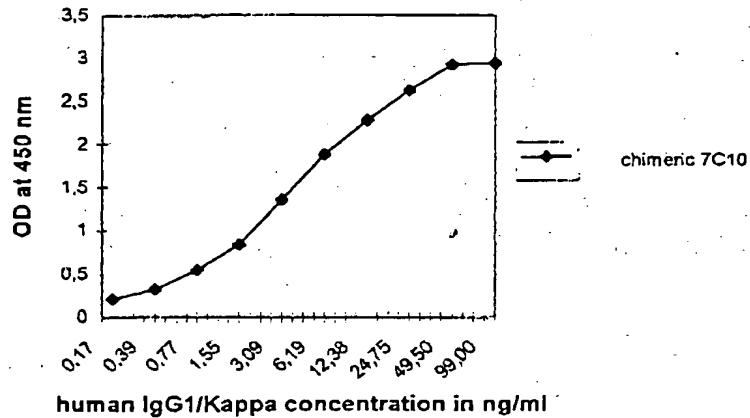


FIGURE 16

CDR 1

7C10 VL mouse	<u>D</u> <u>V</u> <u>L</u> <u>M</u> <u>T</u> <u>Q</u> <u>I</u> <u>P</u> <u>L</u> <u>S</u> <u>L</u> <u>P</u> <u>V</u> <u>S</u> <u>L</u> <u>G</u> <u>D</u> <u>Q</u> <u>A</u> <u>S</u> <u>I</u> <u>S</u> <u>C</u>	R <u>S</u> <u>S</u> <u>Q</u> <u>S</u> <u>I</u> <u>V</u> <u>H</u> <u>S</u> <u>N</u> <u>G</u> <u>N</u> <u>T</u> <u>L</u> <u>Q</u>
DRB1-4.3	<u>T</u>
C94-5B11' CL	<u>T</u>
Kabat sgII mouse	<u>V</u>	<u>T</u>
		<u>L</u>
		<u>E</u>

CDR 2

7C10 VL mouse	<u>W</u> <u>Y</u> <u>L</u> <u>Q</u> <u>K</u> <u>P</u> <u>G</u> <u>Q</u> <u>S</u> <u>P</u> <u>K</u> <u>L</u> <u>I</u> <u>Y</u>	K <u>V</u> <u>S</u> <u>N</u> <u>R</u> <u>L</u> <u>Y</u>	G <u>V</u> <u>P</u> <u>D</u> <u>R</u> <u>F</u> <u>S</u> <u>G</u> <u>S</u> <u>G</u> <u>T</u> <u>D</u> <u>F</u> <u>L</u>
DRB1-4.3	F <u>S</u>
C94-5B11' CL	F <u>S</u>
Kabat sgII mouse	F <u>S</u>

CDR 3

7C10 VL mouse	<u>K</u> <u>I</u> <u>S</u> <u>S</u> <u>V</u> <u>E</u> <u>A</u> <u>E</u> <u>D</u> <u>L</u> <u>G</u> <u>V</u> <u>Y</u> <u>C</u>	F <u>Q</u> <u>G</u> <u>S</u> <u>H</u> <u>V</u> <u>P</u> <u>W</u> <u>T</u>	F <u>GG</u> <u>G</u> <u>T</u> <u>K</u> <u>L</u> <u>E</u> <u>I</u> <u>K</u>
DRB1-4.3	... <u>R</u> <u>F</u> ...	<u>S</u> ... <u>D</u> ...
C94-5B11' CL	... <u>R</u>
Kabat sgII mouse	... <u>R</u> <u>T</u> ... <u>Y</u>

FIGURE 17

CDR 1

7C10 VL mouse	DVLMTQIPLSLPVSLGDQASISC	<u>RSSQSIVHSNGNTYLO</u>
GM607	.IV...S.....TP.EP.....	LL....YN..D
DPK15/A19	.IV...S.....TP.EP.....	LL....YN..D
Kabat sgII hu	.IV...S.....TP.EP.....	LL..D.XX..X

CDR 2

7C10 VL mouse	WYLQKPGQSPKLLIY	<u>KVSNRLY</u>	GVPDRFSGSGSGTDFTLK
GM607Q....	LG....AS
DPK15/A19Q....	LG....AS
Kabat sgII huQ....	L....AS

CDR 3

7C10 VL mouse	ISSVEAEDLGVYYC	<u>FQGSHVPWT</u>	FGGGTKLEIK
GM607	..R.....V.....	<u>M.ALQT.Q...</u>	Q...V...
DPK15/A19	..R.....V.....	<u>M.ALQT.</u>	
Kabat sgII hu	..R.....V.....	<u>M.ALQX.R...</u>	Q...V...

FIGURE 18

CDR 1

7C10 VL mouse	DVLMTQIPLSLPVSLGDQASISC	<u>RSSQSIVHSNGNTYLO</u>
GM 607	.IV...S.....TP.EP.....	LL....YN..D
7C10 VL Humanized 1	..V...S.....TP.EP.....	
7C10 VL Humanized 2	.IV...S.....TP.EP.....	

CDR 2

7C10 VL mouse	WYLQKPGQSPKLLIY	<u>KVSNRLY</u>	GVPDRFSGSGSGTDFTL
GM 607Q....	LG....AS
7C10 VL Humanized 1Q....
7C10 VL Humanized 2Q....

CDR 3

7C10 VL mouse	KISSVEAEDLGVYYC	<u>FQGSHVPWT</u>	FGGGTKLEIK
GM 607	...R.....V.....	<u>M.ALQT.Q...</u>	Q...V...
7C10 VL Humanized 1	...R.....V.....	Q...V...
7C10 VL Humanized 2	...R.....V.....	Q...V...

FIGURE 19

MluI

1 GTCACAAACGCCTGCCACCATGAAGTCCCTGTTAGGCTGTTGGTGTATGTTCTGG
1 CAGTCTTGGCAGCCCCGGTGGTACTTCAACGGACAATCCGACAACCACGACTACAAGACC 60

M K L P V R L L V L M F W -

Peptide leader

61 TTTCTGCTTCCAGCAGTGTGATGATGACTCAGTCTCCACTCTCCCTGCCCGTCACC
61 AAAGGACGAAGGTCTGCACTACAAACACTACTGAGTCTAGAGGTCAGAGGGACGGGCAGTGG 120

2 F P A S S S D V V M T O S P L S L P V T -

121 CCTGGAGAGCCGGCCTCCATCTCTGCAGGTCTAGTCAGAGCATTGTACATAGTAATGGA
121 GGACCTCTCGGCCGGAGGTAGAGGACGTCCACATCAGTCTGTAACATGTATCATTACCT 180

CDR 1

P G E P A S I S C R S S Q S I V H S N G -

KpnI

181 AACACCTATTGCAATGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTGATCTAT
181 TTGGTGGATAAACGTTACCATGGACGTCTCCGTCCGTAGAGGTGTCGACCTAGATA 240

N T Y L Q W Y L Q K P G Q S P O L L I Y -

AAAGTTCTAATCGGCTTATGGGTCCCTGACAGGTTCAGTGGCAGTGCATCAGGCACA
241 TTTCAAAGATTAGCCGAAATACCCCAGGGACTGTCCAAGTCACCGTCACCTAGTCCGTCT 300

CDR 2

K V S N R L Y G V P D R F S G S G S G T -

301 GATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATCTGGGGTTATTACTGCTTT
301 CTAAAATCTGACTTTAGTCGTCACCTCCGACTCCTACAACCCCAAATAATGACGAAA 360

D F T L K I S R V E A E D V G V Y Y C F -

361 CAAGGTTACATGTTCCGTGGACGTTGGCCAAAGGGACCAAGGTGAAAATCAAACGTGAG
361 GTTCCAAGTGTACAAGGCACCTCCAAGCCGGTCCCTGGTCCACCTTAGTTGCACTC 420

CDR 3

O G S H V P W T F G Q G T K V E I K

BamHI

421 TGGATCCTCTGCG 433

ACCTAGGAGACGC

FIGURE 20

MluI

1 CTCAGAACGCCTGCCACCATGAAGTTGCCTGTTAGGCTGTTGGTGTATGTTCTGG
1 CAGTCTTGCCTGCCACGGCGGTGGTACTTCACACGACAATCCGACAACCACGACTACAGACC 60

2 M K L P V R L L V L M F W -
Leader peptide

61 TTTCCCTGCTTCCAGCAGTGTATATTGTGATGACTCAGTCTCCACTCTCCCTGCCGTACCC
61 AAAGGACGAAGGTGCTCACTACACACTACTGAGTCAGAGGTGAGAGGGACGGGAGTGG 120

2 F P A S S S D I V M T Q S P L S L P V T -
121 CCTGGAGAGGCCGGCTCCATCTCTGCAGGTCTAGTCAGAGCATTGTACATAGTAATGGA
121 GGACCTCTCCCCCCCAGGTAGAGGACGTCCAGATCAGTCTCGTAACATGTATCATTACCT 180

2 CDR 1
P G E P A S I S C R S S Q S I V H S N G -
KpnI

181 AACACCTATTTGCAATGGTACCTGCAGAACGCCAGGGCAGTCTCCACAGCTCCTGATCTAT
181 TTGTGGATAAACGTTACCATGGACGTCTCCGTCCCGTCAGAGGTGTCGAGGACTAGATA 240

2 N T Y L C W Y L Q K P G Q S P Q L L I Y -
241 AAAGTTCTAATCGGCTTATGGGGTCCCAGACAGGTTCACTGGCAGTGGATCAGGCACA
241 TTTCAGAGATAGCCGAAATACCCCAAGGGACTGTCCAAGTCACCGTCACTAGTCCGTGT 300

2 CDR 2
K V S N R L Y G V P D R F S G S G S G T -
301 GATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTCCGGTTATTACTGCTTT
301 CTAAAGATGTGACTTTAGTCGTCTCACCTCCACTCCTACACCCCAAATAATGACGAAA 360

2 D F T L K I S R V E A E D V G V Y Y C F -
361 CAAGGTTCACATGTTCCGTGGACGTTGGCCTAACGGACCAAGGTGGAAATCAAACCTGAC
361 GTTCCAAGTGTACAAGGCACCTGCAAGGCCGGTCCCTGGTTCCACCTTAGTTGCACTC 420

2 CDR 3
Q G S H V P W T F G Q G T K V E I K
BamHI

421 TGGATCCTCTGCG 433
421 ACCTACGGAGACGC

FIGURE 21

17 27 CDR 1
7C10 VH DVQLQESGPGLVKPSQSLSLTCSVTGYSIT GGYLWN WIRQ
AN03' CL S..Y..
Kabat sgI(A) E.....S.....T.....D... S..WN. ...

CDR 2
7C10 VH FPGNKLEWMG YISYDGTNNYKPSLKD RISITRDTSKNQFFL
AN03' CL N...N...N...N ..
Kabat sgI(A) S.STY.N...S Y..

84 CDR 3
7C10 VH KLNSVTNEDTATYYCAR YGRV-FFDY WGQGTTLT^VS
AN03' CL T..... E.YGY.....
Kabat sgI(A) Q.....T..... G.YGYG.....V....

FIGURE 22

Rch 1 30 CDR 1 Rch 2
7C10 VH mouse DVQLQESGPGLVKPSQSLSLTCSVTGYSIT GGYLWN WIRQ
human Kabat sgII Q.....T.....T.S.G.VS SYWS..
human VH FUR1' CL Q.....ET.....T.S....S S..Y.S ..
human Germeline Q.....ET.....T.S....S S..Y.S ..

Rch 2 48 CDR 2 67 71 Rch 3
7C10 VH mouse FPGNKLEWMG YISYDGTNNYKPSLKD RISITRDTSKNQFFL
human Kabat sgII P..KG...I. R.Y.S.STX.N....S .VT.SV.....S.
human VH FUR1' CL P..KG...I. SMFHS.SSY.N....S .VT.SV.....S.
human Germ-line P..KG...I. S.YES.STY.N....S .VT.SV.....S.

Rch 3 CDR 3 Rch 4
7C10 VH mouse KLNSVTNEDTATYYCAR YGRVFFDY WGQGTTLT^VS
human Kabat sgII ..S...AA...V..... ELPGGYDVLV....
human VH FUR1' CL Q.R...AA...V..... GRYCSSTSCNWFDPLV....
human Germeline ..S...AA...V.....

FIGURE 23

	30 CDR 1	48
7C10 VH mouse	DVQLQESGPGLVKPSQSLSLTCVTGYSIT	<u>GGYLWN</u> WIRQFPGNKLEWMG
human germline	Q.....	ET.....T.S.... <u>S</u> S..Y.GP..KG... <u>I</u> .
VH Humanized 1	Q.....	ET.....T.S.....P..KG.....
VH Humanized 2	Q.....	ET.....T.S.....P..KG...I.
VH Humanized 3	Q.....	ET.....T.S.... <u>S</u>P..KG...I.
CDR 2		67 71
7C10 VH mouse	<u>YISYDGTNNYKPSLKD</u>	RISITRDTSKNQFFLKLNSVTNEDTATYYCAR
human germline	<u>S.FHS.SSY.N....S</u>	<u>VT.SV</u>S...S...AA...V.....
VH Humanized 1T.S.....S...S...AA...V.....
VH Humanized 2	<u>VT.S</u>S...S...AA...V.....
VH Humanized 3	<u>VT.SV</u>S...S...AA...V.....
CDR 3		
7C10 VH mouse	<u>YGRVFFDY</u>	WGQGTTLTVSS
human germlineLV....
VH Humanized 1LV....
VH Humanized 2LV....
VH Humanized 3LV....

FIGURE 24

MluI

1 GTCAGAACGCGTGCCGCCACCATGAAAGTGTGAGTCTGTTGTACCTCTTGACACCCATT 60
1. CAGTCTTGCACGGCGGTGGTACTTCACAACTCAGACAACTGGAGAACTGTCGGTAA

M K V L S L L Y L L T A I -
Leader peptide

161 CCTGGTATCCTGTCTCAGGTGCAGCTTCAGGAGTCGGGGCCAGGACTGGTGAAGCCTCG 120
GGACCATAGGACAGAGTCCACGTGAAAGTCTCAGCCGGTCTGACCACTTCGGAAGC

E G I L S Q V Q L Q E S T P G L V K P S -
121 GAGACCCCTGTCCTCACCTGCACTGTCTCTGGTTACTCCATCACCCGTCCTTATTTATGG 180
CTCTGGGACAGGGAGTGGACGTGACAGAGACCAATGAGGTAGTGGCCACCAATAATACC
30 CDR 1
E T L S L T C T V S G Y S T T G G Y L W -
181 AACTGGATAACGGCAGCCCCCAGGGAGGGACTGGAGTCGATGGGTATATCAGCTACGAC 240
TTGACCTATGCCGTGGGGTCCCTTCCCTGACCTCACCTACCCCCATATACTCGATGCTG
48

N W I R Q P P G K G L E W M G Y I S Y D -
KpnI
GGTACCAATAACTACAAACCCCTCCCTCAAGGATGAAATCACCATATCACGTGACACGTCC 200
241 CCATGGTTATTGATGTTGGGAGGGACTTCCTAGCTTAGGGTATACTGCACTGTGCAGG 300
CDR 2 67 71
G T N N Y K P S L K D R I T I S R D T S -
301 AAGAACCGAGTTCTCCCTGAAGCTGAGCTCTGTGACCGTGCAGGACACTGCAGTGTATTAC 360
TTCTGGTCAAGAGGGACTTCGACTCGAGACACTGGCGACGCCGTGACGTACATAATG
K N Q F S L K L S S V T A A D T A V Y Y -
TGTGGAGAGATACGGTAGGGTCTTCTTGACTACTGGGGCAGGGAACCCCTGGTACCGTC 420
361 ACACGGCTCATGCCATCCAGAAGAAACTGATGACCCUGTCCCTGGGACCGAGTGGCAG
CDR 3
C A R Y G R V F F D Y W G Q G T L V T V -
BamHI
1421 TCCTCAGGTGAGTGCATCCTCTGCG 445
AGGAGTCCACTCACCTAGGAGACGC

S S -

FIGURE 25

MluI

1 GTCAGAACCGCGTGCCGCCACCATGAAAGTGTGAGTCTGTTGTACCTCTTGACAGCCATT
 60 CAGTCTTGGCCACGGCGGTGGTACTTTACAACTCAGACAACTGGAGAACTGTCGGTAA

M K V L S L L Y L L T A I
 Leader peptide

21 CCTGGTATCCTGTCTCAGGTGCAGCTTCAGGAGTCGGGCCAGGACTGGTGAAGCCTTCG
 120 GCACCATACCAACAGAGTCCACGTCGAAGTCCTCAGCCCGGGTCTGACCAACTTCGGAAGC

P G I L S Q V Q L Q E S G P G L V K P S -

121 GAGACCCCTGTCCTCACCTGCACTGTCTGTTACTCCATCACCGGTGCTTATTATCG
 180 CTCTGGACAGGGAGTGGACGTGACAGAGACCAATGAGCTAGTCGCCACCAATAATACC
 30 CDR 1
 E T L S L T C T V S G Y S I T G G Y L W -

181 AACTCCATAACGGCAGCCCCAACCGAAGGGACTGGAGTGGATCCCTATATCAGCTACGAC
 240 TTGACCTATGCCGTCCCCGGTCCCCCTGACCTCACCTAGCCCATATAGTCGATGCTG
 48
 N W I R Q P P G K G L E W I G Y I S Y D -

KpnI

241 GGTACCAATAACTACAAACCCCTCCCTCAAGGATCGAGTCACCATATCACGTGACACGTCC
 300 CCATGGTTATTGATGTTGGAGGGAGTCCCTAGCTCAGTCCTAGTCGACTGTGCAGG
 CDR 2
 67 71
 G T N N Y K P S L K D R V T I S R D T S -

301 AAGAACCAAGTTCTCCCTGAAGCTGAGCTCTGTGACCCCTCGGGACACTGCACTGTATTAC
 360 TTCTTGGTCAAGAGGGACTTCGACTCGAGACACTGGCGACGCCGTGACGTACATAATG
 K N Q F S I K I S S V T A A D T A V Y Y -

361 TGTGGAGATAACGGTAGGGCTTCTTGACTACTGGGCCAGGGAACCCCTGCTACCGTC
 420 ACACCCCTCATGCCATCCCAGAAGAAACTGATGACCCCCGGTCCCTGGGACAGGGCAG
 CDR 3
 C A R Y C R V F E D Y W G Q G T L V T V -

BamIII

421 TCCTCAGGTGAGTGGATCCTCTGCG
 445 AGGAGTCCACTCACCTAGGAGACGC

S S -

FIGURE 26

MluI

1 CTCAGAACGCGTGCCGCCACCATGAAAGTGTGAGTCTGTTGACCTCTGACAGCCATT
 1 CAGTCTTGGCACGGCGGTGGTACTTTCACAACTCACACACATGGAGAACTGTCGGTAA

M K V L S L L Y L L T A I -
 Leader peptide

61 CCTGGTATCCTGTCTCAGGTGCAGCTTCAGGAGTCGGGCCAGGACTGGTGAAGCCTTCG
 61 GGACCATAGGACAGAGTCCACGTCGAAGTCCCTCAGCCGGTCCCTGACCACTTCGGAAGC

P G I L S Q V Q L O E S G F G L V K P S -
 121 GAGACCCCTGTCCCTCACCTGCACGTCTGTTACTCCATCAGCGTGGTTATTATGG
 121 CTCTGGGACAGGGAGTGGACGTGACAGAGACCAATGAGGTAGTCGCACCAATAAATACC
 30 CDR 1
 E T L S L T C T V S G Y S I S G G Y I W -
 181 AACTGGATACGGCAGCCCCCAGGGAAACCCACTGGAGTGGATCGGGTATATCAGCTACGAC
 181 TTGACCTATGCCGTGGGGTCCCTCCCTGACCTCACCTACCCATATACTGCGATGCTG
 48
 N W I R Q P P G K G L E W I G Y I S Y D -
 KpnI
 241 GGTACCAATAACTACAAACCCCTCCCTCAAGGATCGAGTCACCATATCAGTGGACACGTCC
 241 CCATGGTTATTGATGTTGGGAGGGATTCCCTAGCTCAGTGGTATAGTCACCTGTGCAGG
 67 71
 C T N N Y K P S L K D R Y T I S V D T S -
 301 AAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCCCTGCGGACACTGCAGTGTATTAC
 301 TTCTGGTCAAGAGGGACTTCGACTCGAGACACTGGCGACGCCGTGACGTACATAATG
 360
 K N Q F S L K L S S V T A A D T A V Y Y -
 361 TGTGCGAGATACTGGTAGGGTCTCTTCACTACTGGGGCCAGGGAACCCCTGGTCACCGTC
 361 ACACGCTCTATGCCATCCAGAAGAAACTGATGACCCGGTCCCTGGGACCACTGGCAG
 CDR 3
 C A R Y G R V F F D Y W G Q G T L V T V -
 BamHI
 421 TCCTCAGGTGAGTGGATCCTCTGGC
 421 445
 AGGAGTCCACTCACCTAGGAGACGC
 S S

FIGURE 27

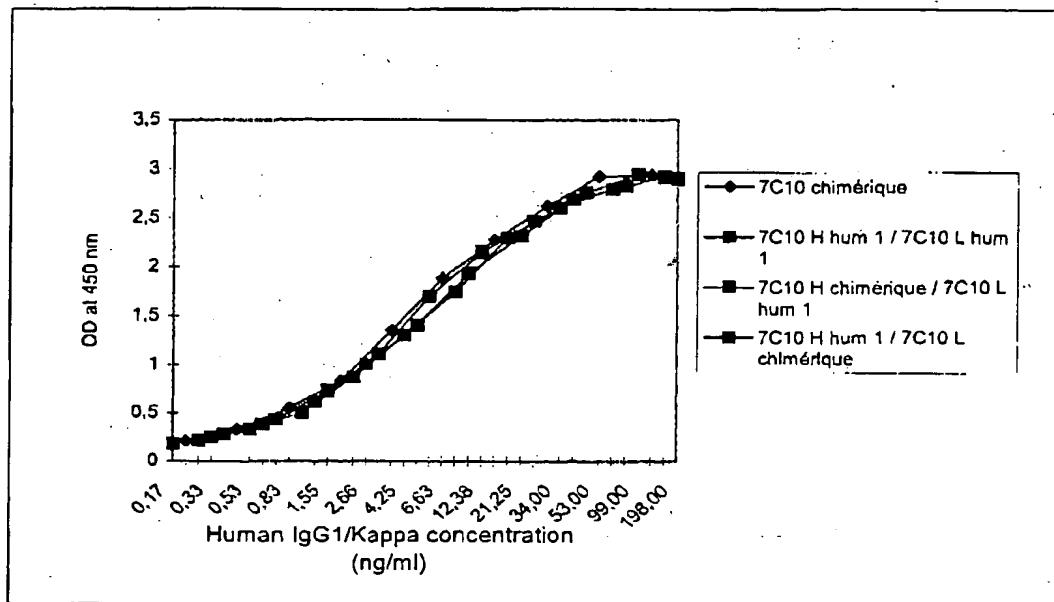


FIGURE 28

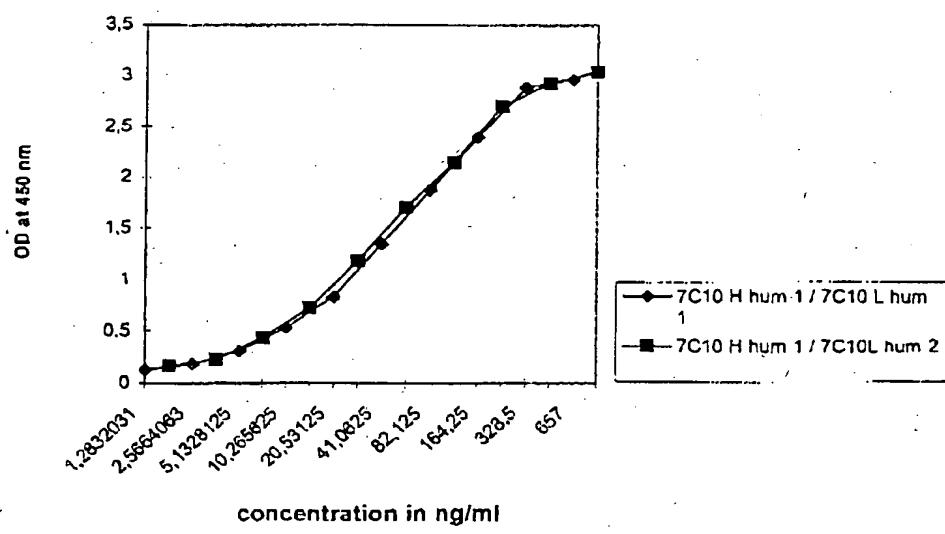


FIGURE 29

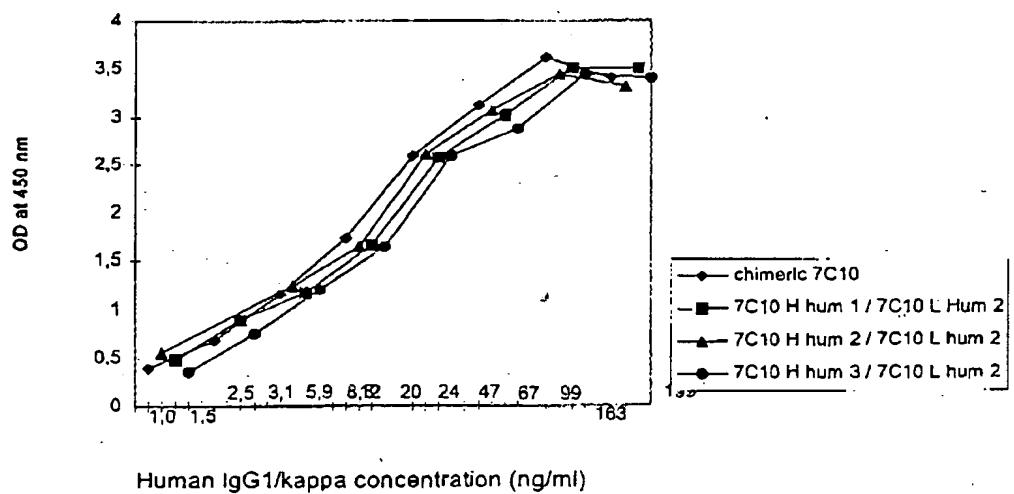
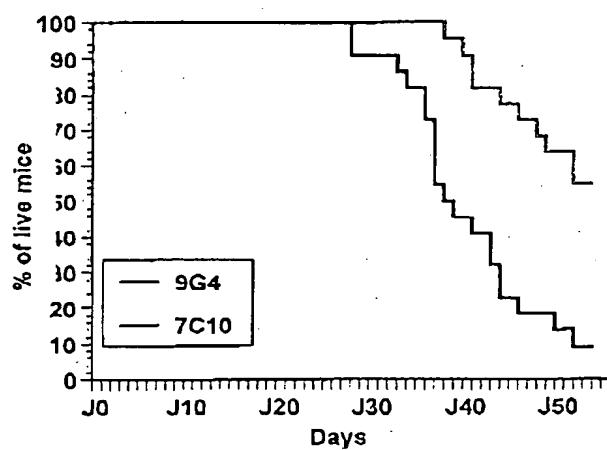


FIGURE 30



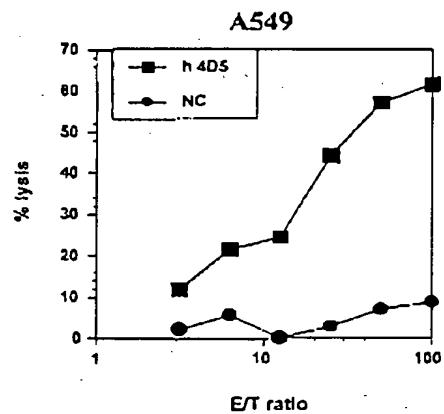


FIGURE 32A

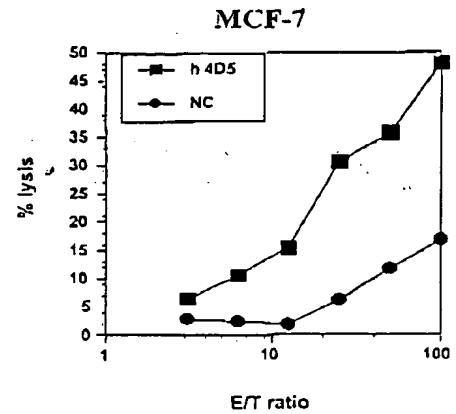


FIGURE 32B

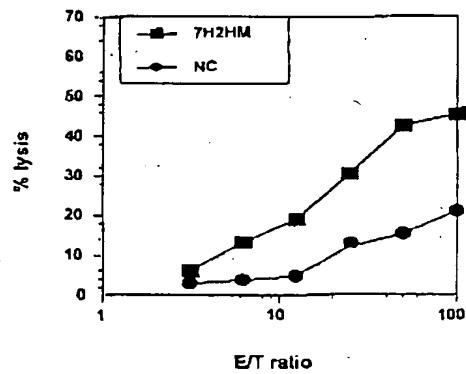


FIGURE 32C

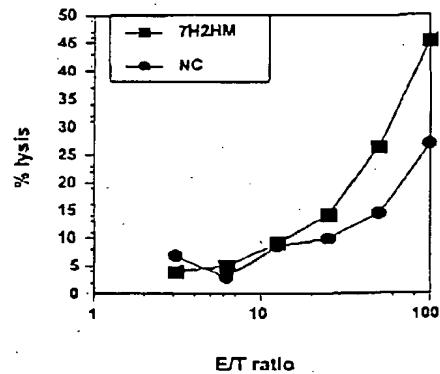


FIGURE 32D

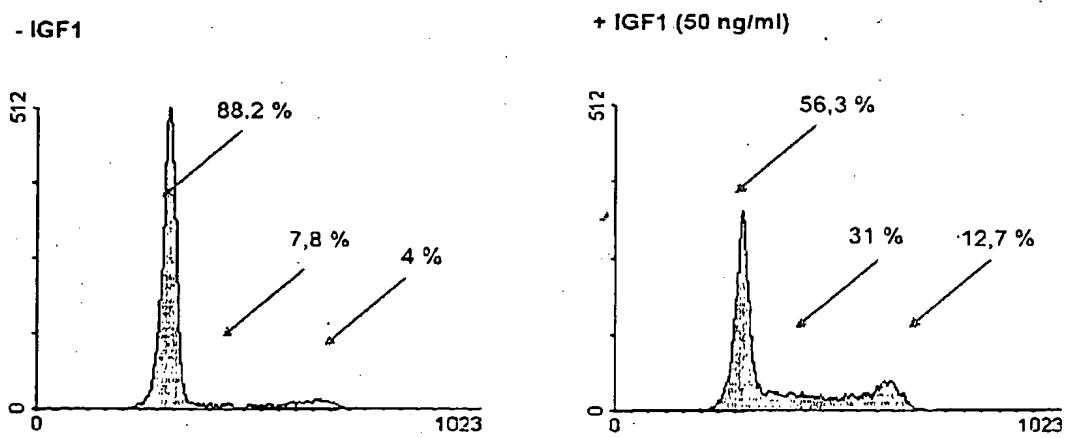


FIGURE 33A

FIGURE 33B

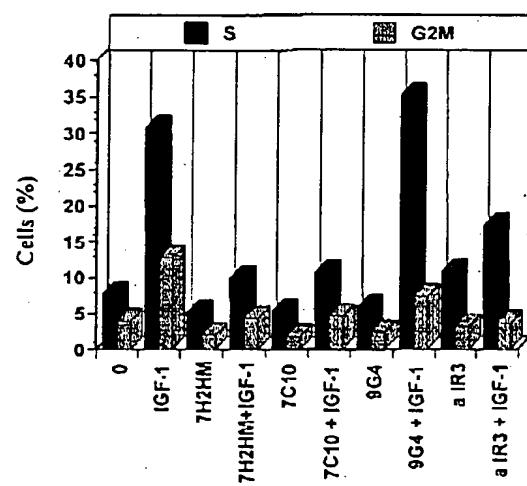


FIGURE 33C

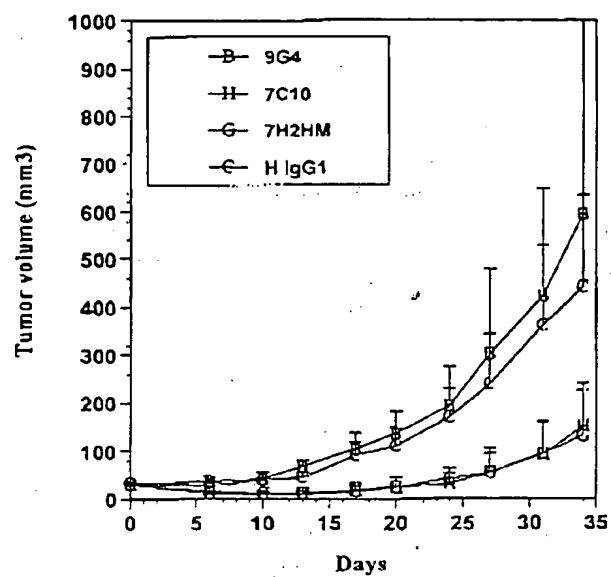


FIGURE 34A

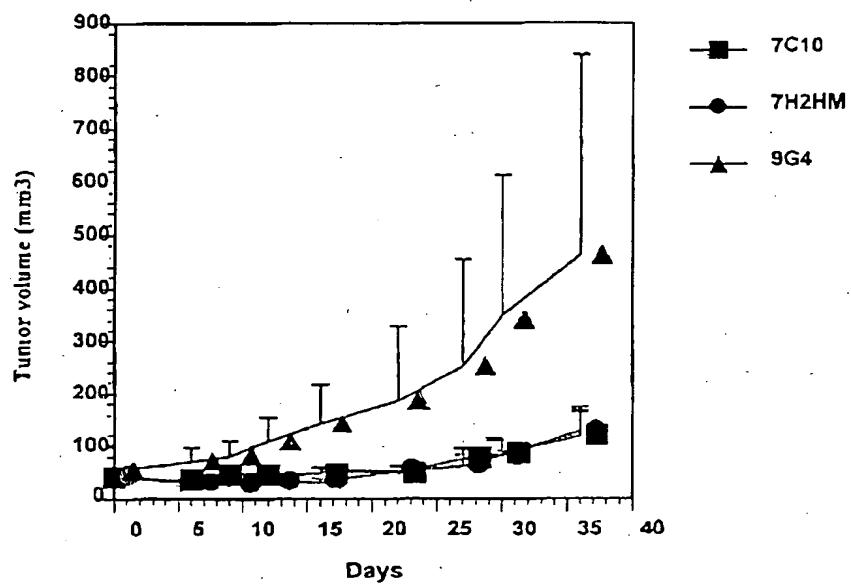


FIGURE 34B

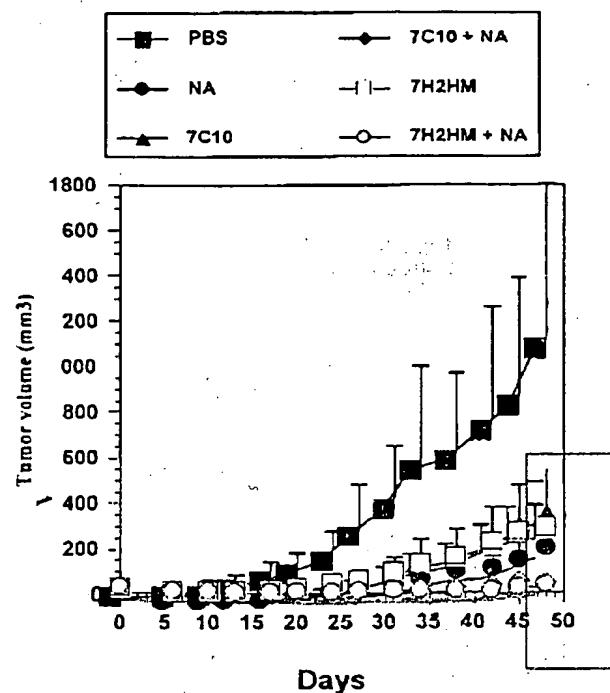


FIGURE 35A

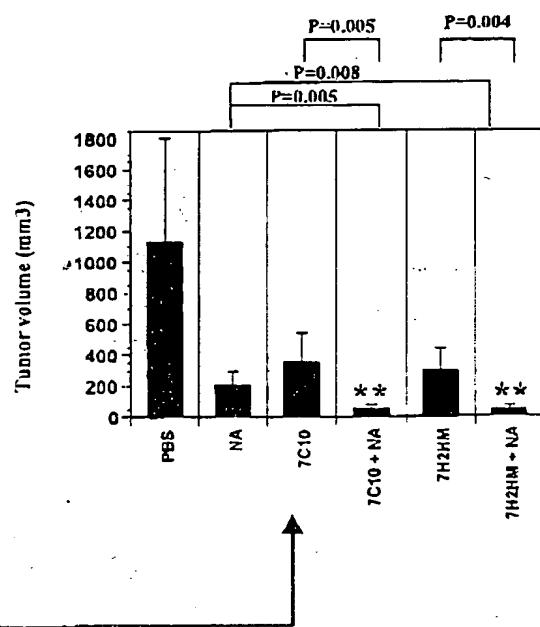


FIGURE 35B

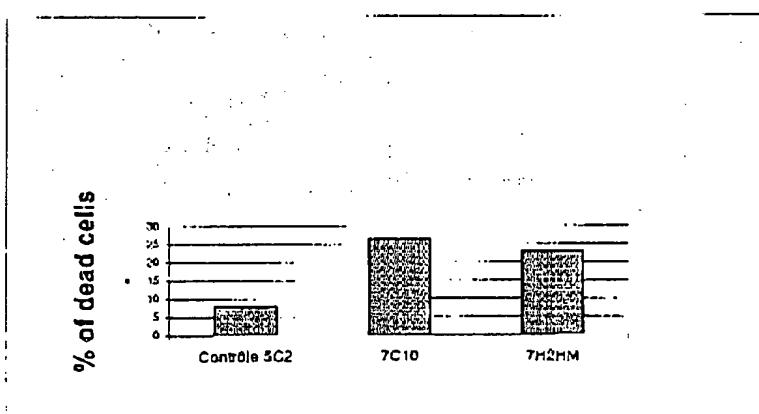


FIGURE 36

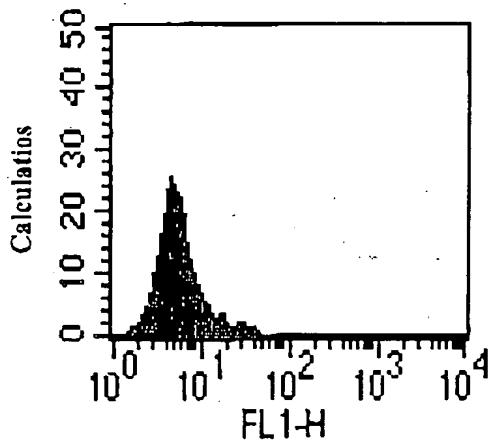


FIGURE 37A

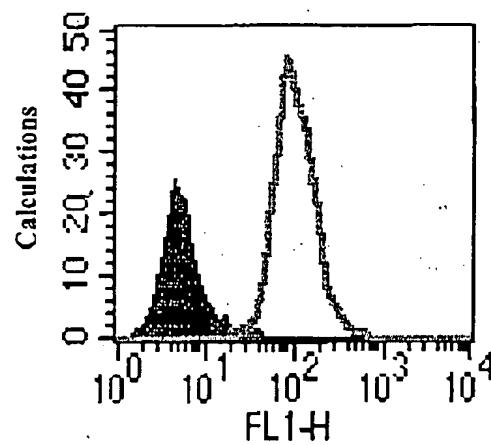


FIGURE 37B

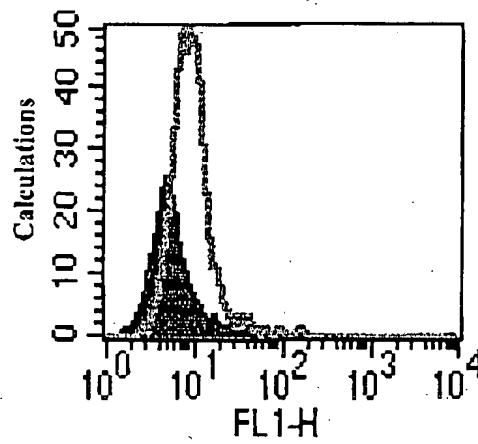


FIGURE 37C

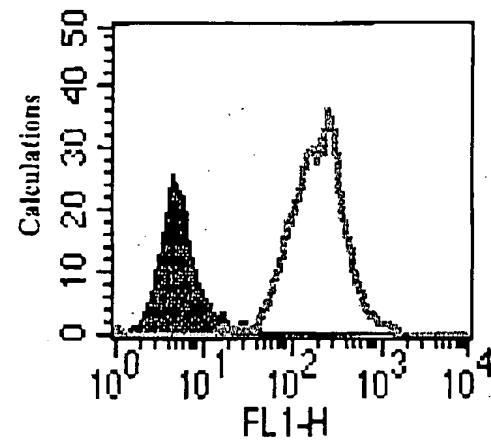


FIGURE 37D

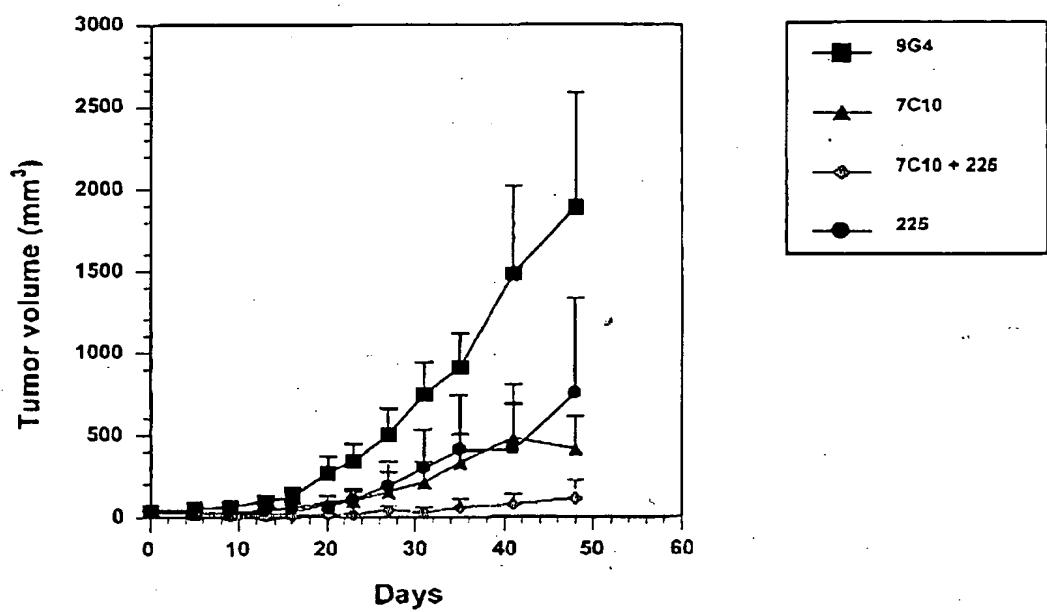


FIGURE 38

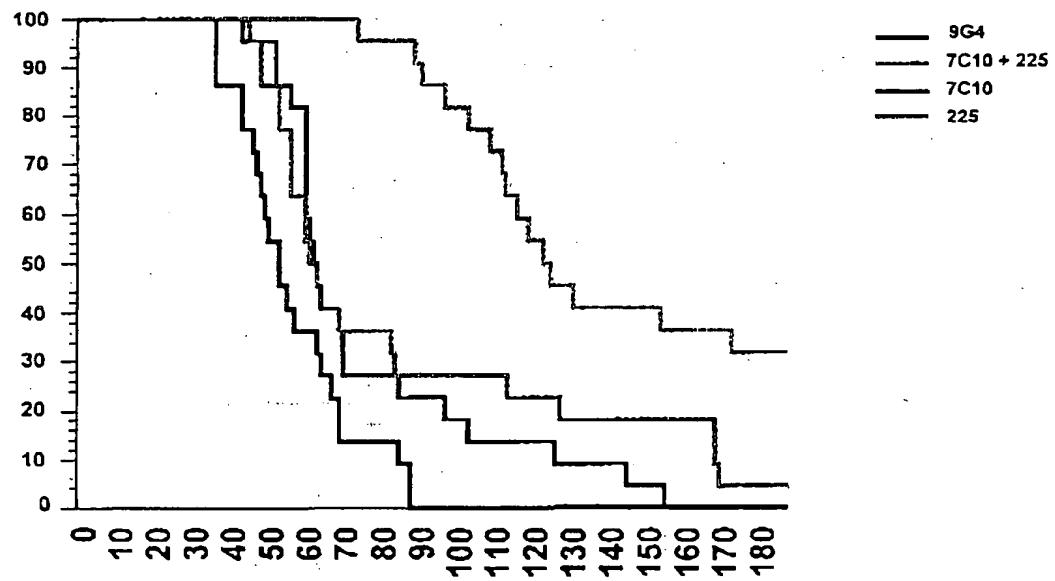


FIGURE 39

FIGURE 40A

IGF-I 50 ng/ml

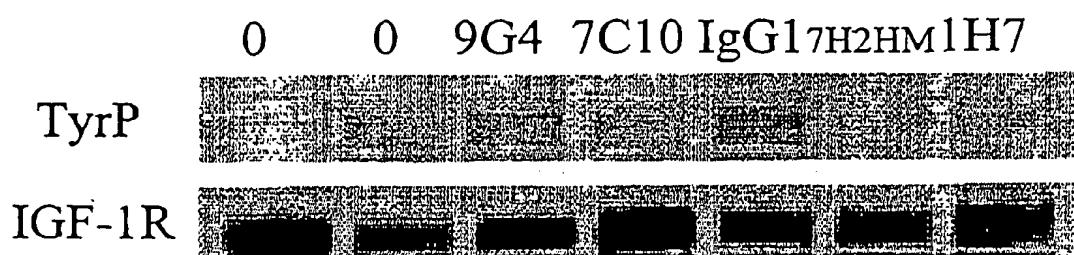


FIGURE 40B

IGF-I 50 ng/ml

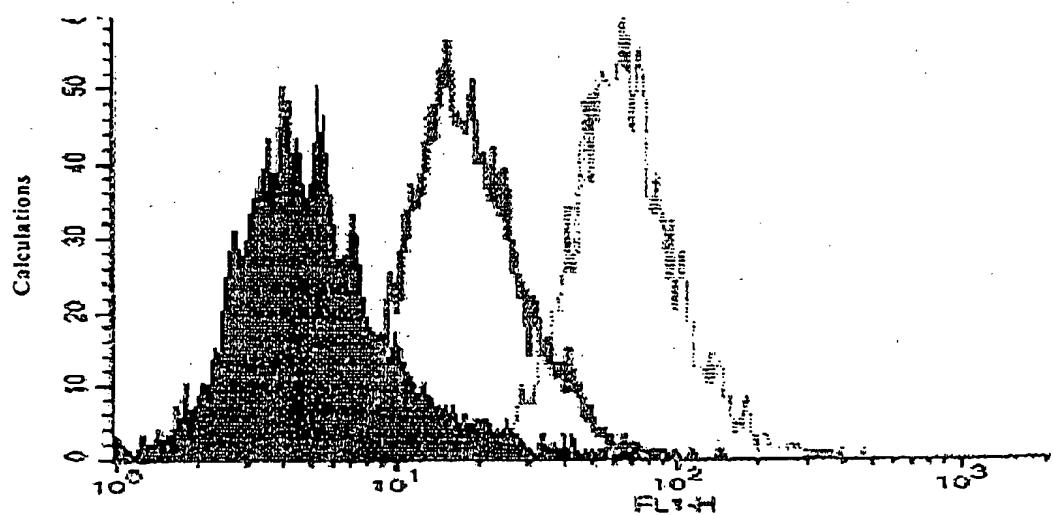
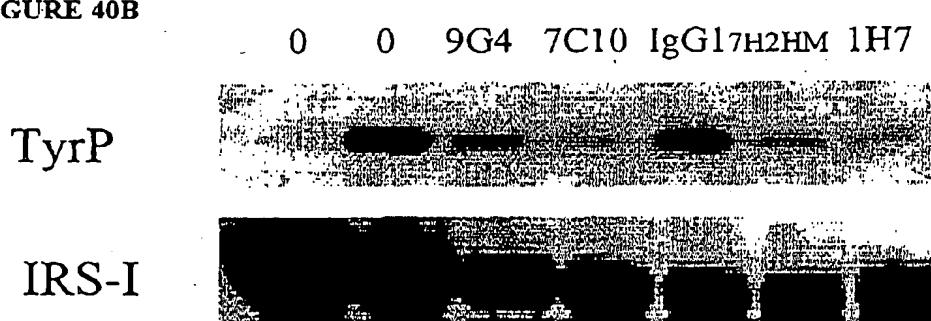


FIGURE 41

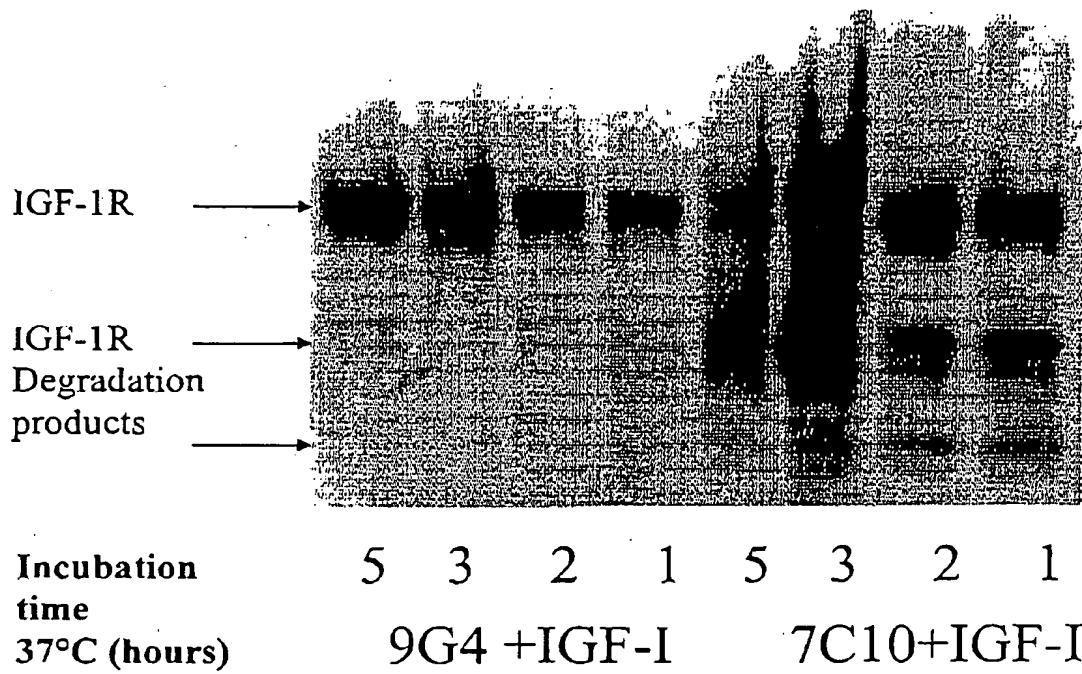


FIGURE 42A

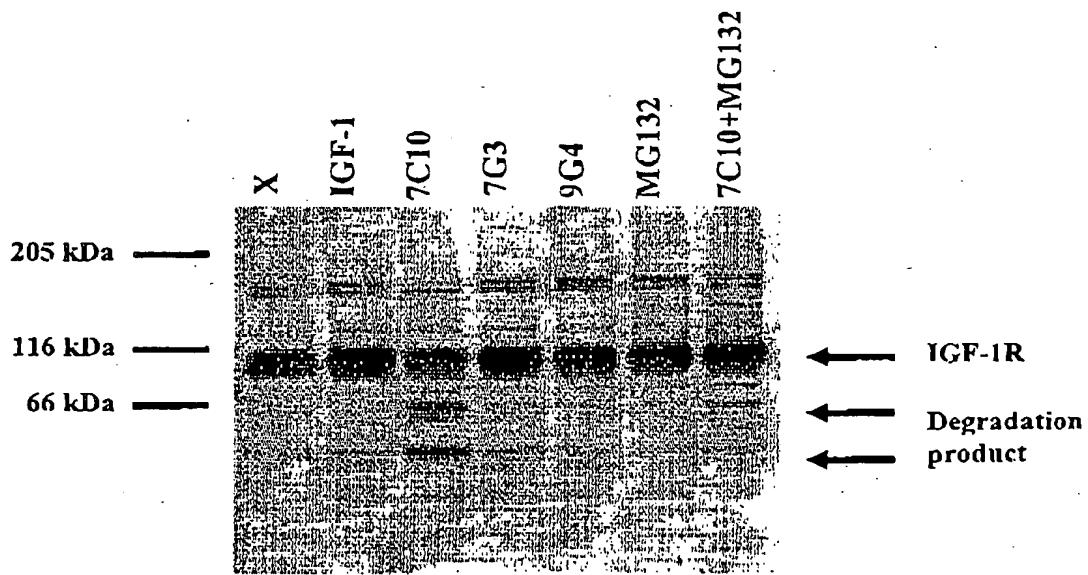


FIGURE 42B

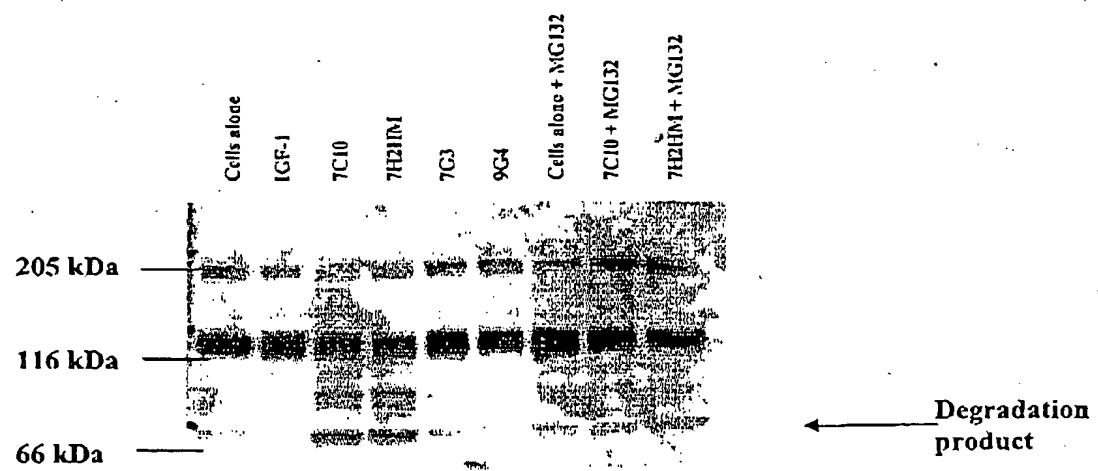


FIGURE 42C

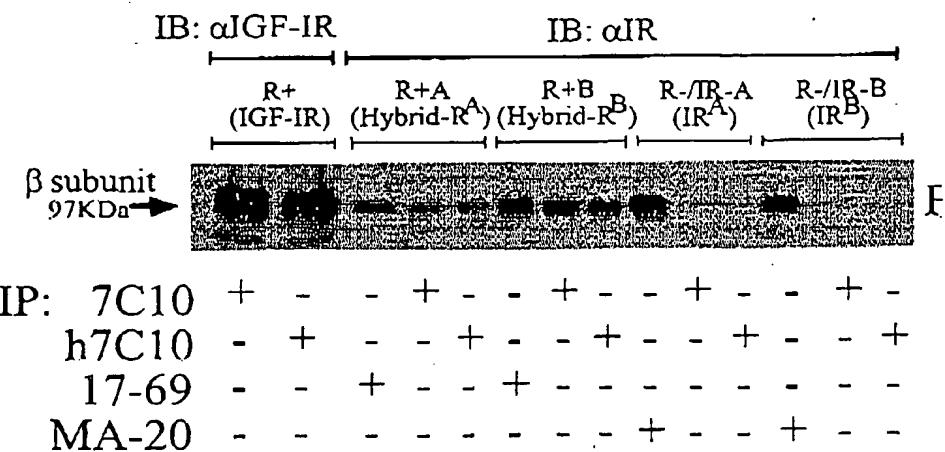


FIGURE 43A

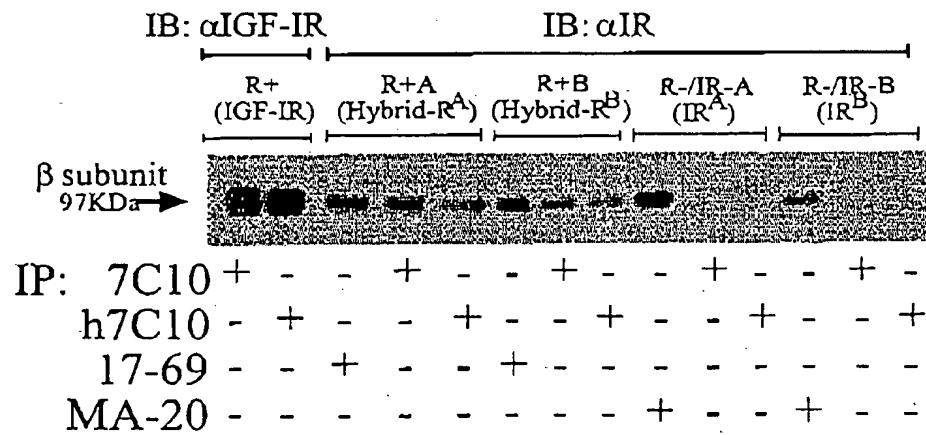


FIGURE 43B

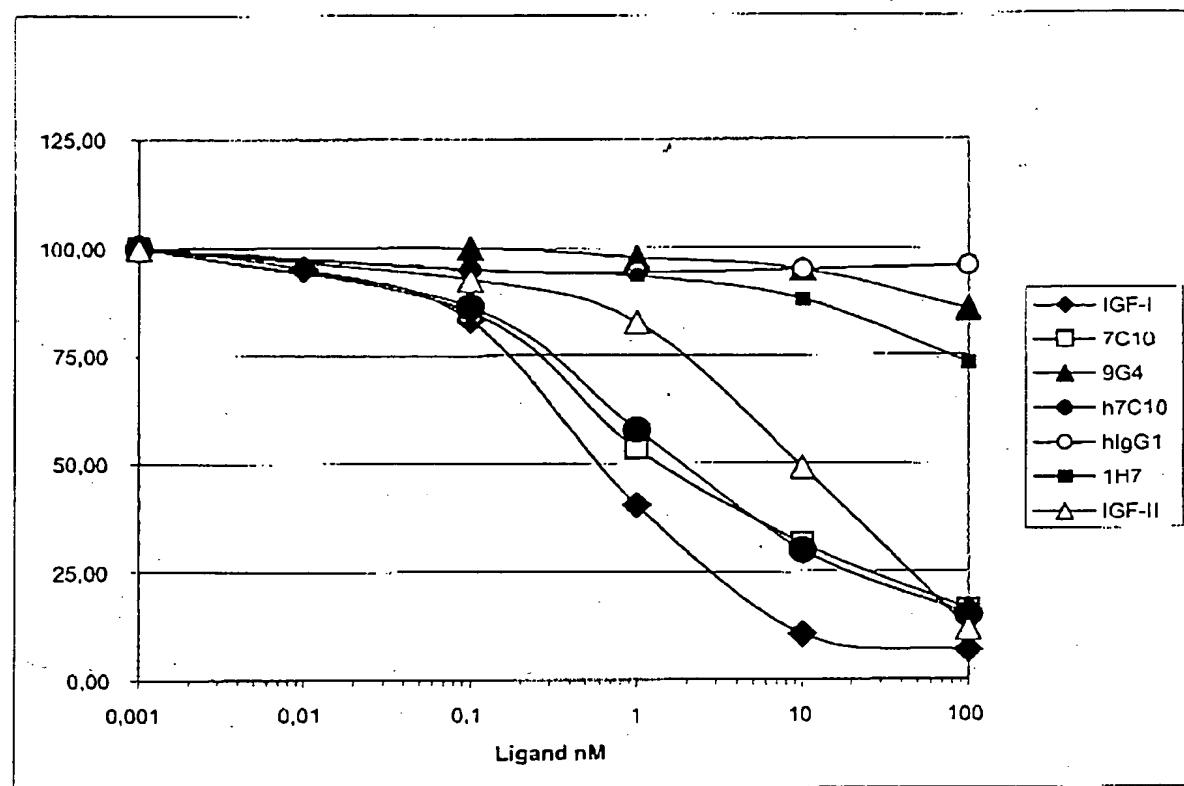


FIGURE 44

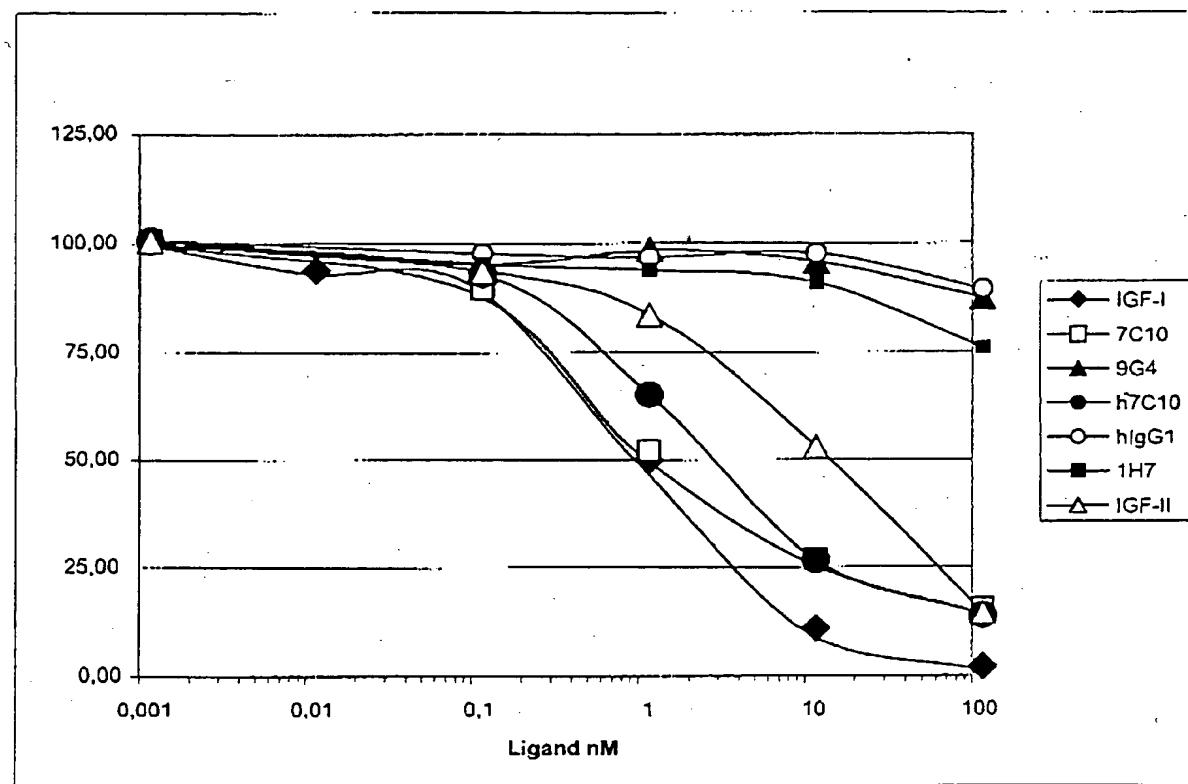


FIGURE 45

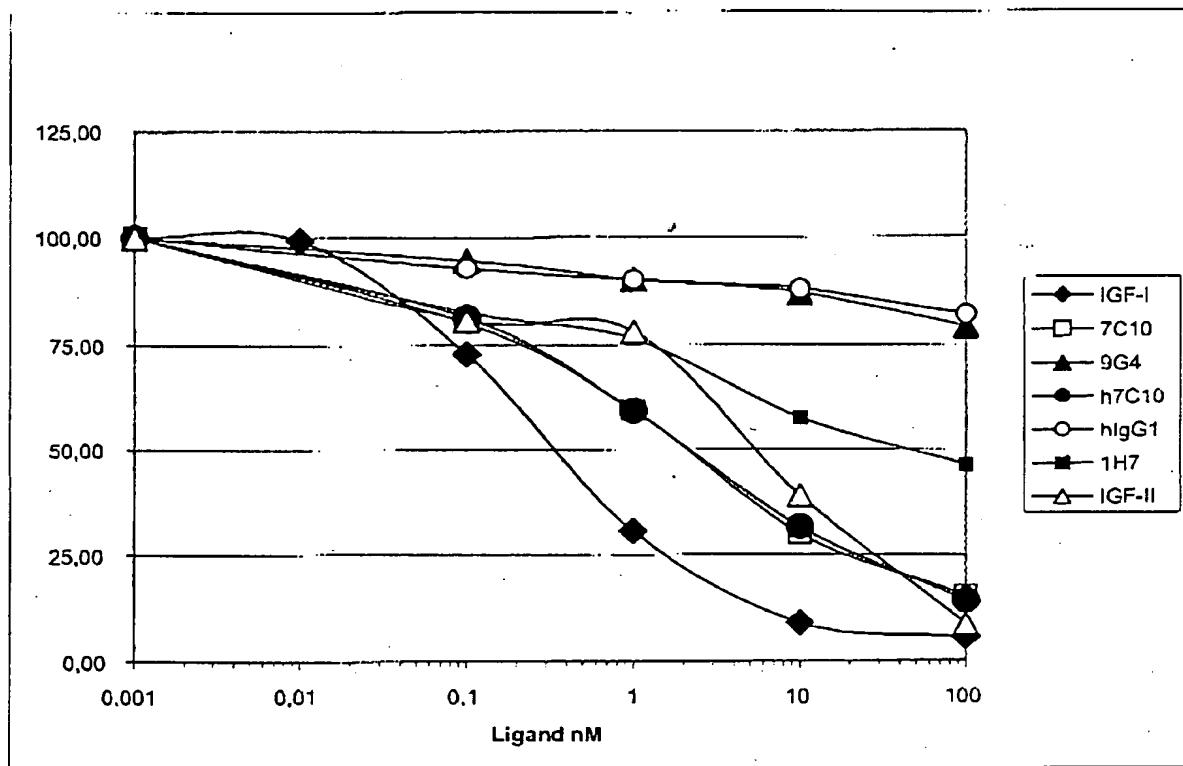


FIGURE 46

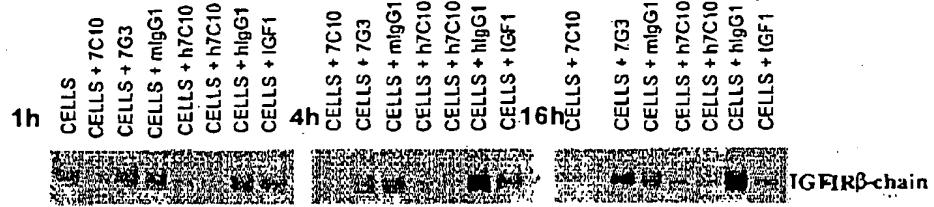


FIGURE 47A

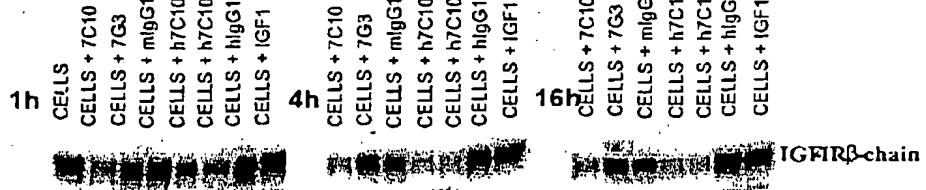


FIGURE 47B

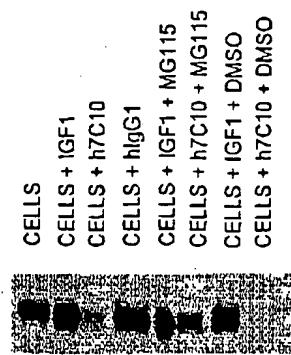


FIGURE 48

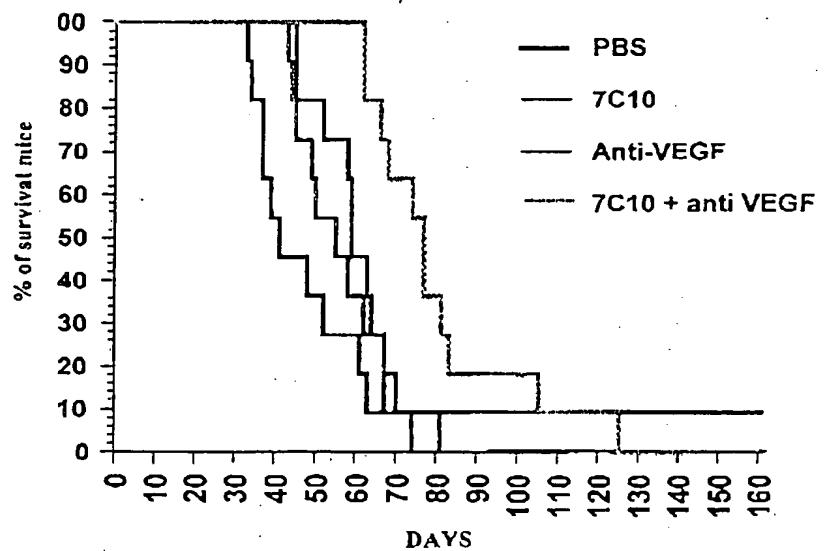


FIGURE 49

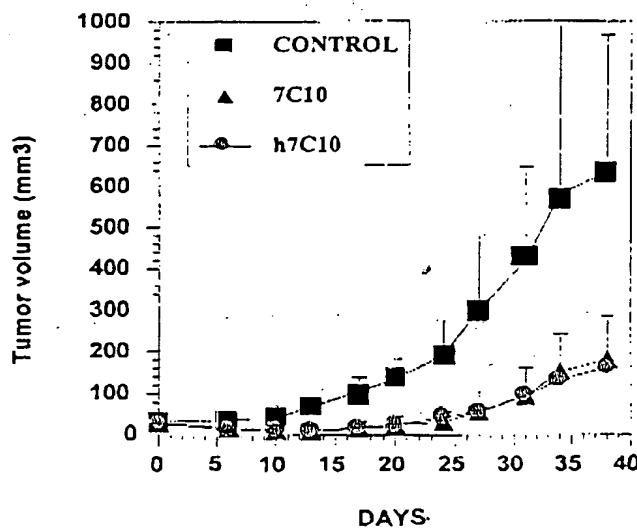


FIGURE 50

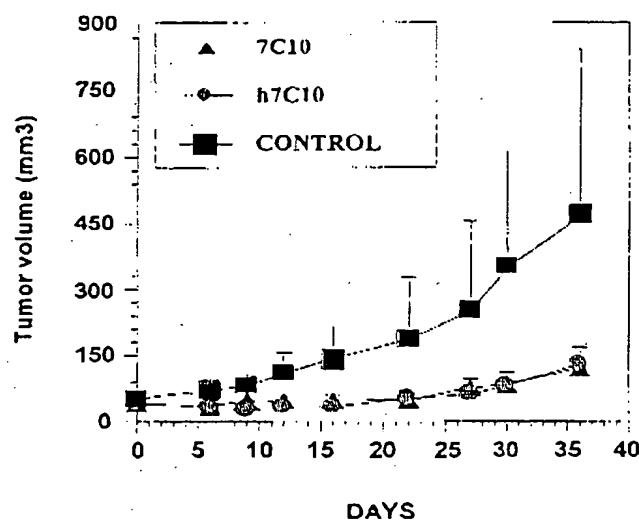


FIGURE 51

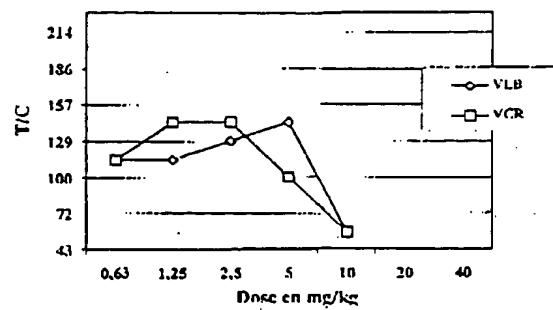


FIGURE 52

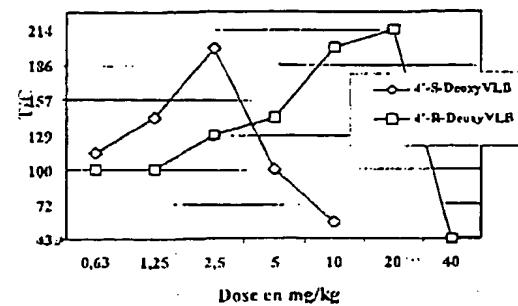


FIGURE 53

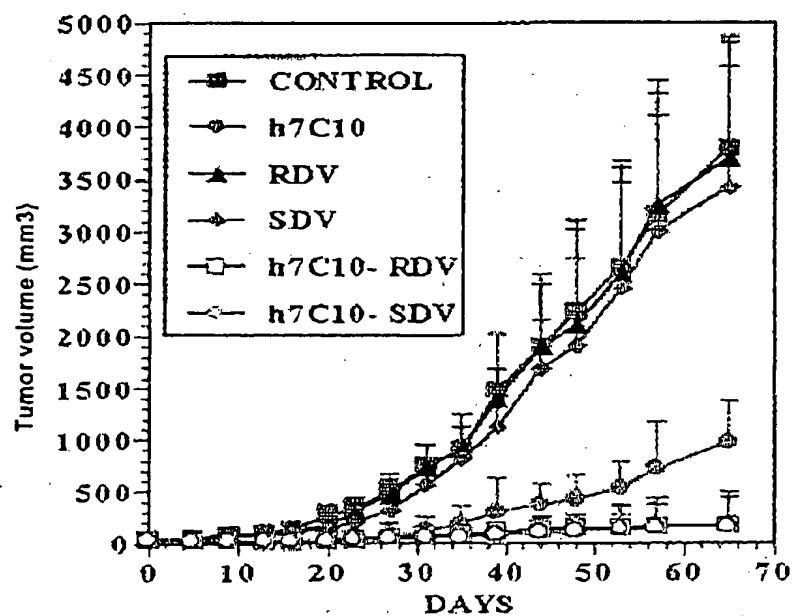


FIGURE 54